PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
2472W00P		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP 98/ 02765	22/06/1998	23/06/1997

Applicant

TAKEDA CHEMICAL INDUSTRIES, LTD. et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 98/02765

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 14 and 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

The present invention relates to a ligand polypeptide prolactin secretion modulating activity, and has a function of modulating placental function.

The ligand polypeptide can be used as a prolactin secretion-stimulating agent for the prevention and treatment of certain diseases associated with prolactin secretion, such as hypoovarianism, gonecyst cacogenesis, menopausal syndrome, euthyroid hypometabolism. In addition, the ligand polypeptide of the invention can be used with advantage as a aphrodisiac.

The ligand polypeptide of the invention can also be used with advantage as a prolactin secretion inhibitory agent in the prevention and treatment of certain diseases associated with prolactin secretion, such as pituitary adenomatosis, brain tumor, emmeniopathy, autoimmune disease, prolactinoma, infertility, impotence, amenorrhea, galactorrhea, acromegaly, Chiari-Frommel syndrome, Argonz-del Castillo syndrome, Forbes Albright syndrome, lymphoma, Sheehan syndrome or dyszoospermia.

In addition, the ligand polypeptide of the present invention is used as an agent for treating or preventing choriocarcinoma, hydatid mole, irruption mole, abortion, unthrifty fetus, abnormal saccharometabolism, abnormal lipidmetabolism or oxytocia.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 98/02765

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/575 C07K14/72 A61K38/22 C07K16/26 C12N15/16
G01N33/74

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data bese end, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriete, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US ZHENG T ET AL: "Phenotypic characterization and functional correlation of alpha- MSH binding to pituitary cells." XP002084795 see abstract & AMERICAN JOURNAL OF PHYSIOLOGY, (1997 FEB) 272 (2 PT 1) E282-7. JOURNAL CODE: 3U8. ISSN: 0002-9513., United States ---	1,4-7, 10-14
X	WO 96 05310 A (UNIV MINNESOTA ;EL HALAWANI MOHAMED E (US)) 22 February 1996 see the whole document --- -/--	1,4-7, 10-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdale of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing dete but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Dale of the actual completion of theinternational search	Date of mailing of the international search report
18 November 1998	02/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	XIE G -X ET AL: "EXPRESSION CLONING OF CONA ENCOOING A SEVEN-HELIX RECEPTOR FROM HUMAN PLACENTA WITH AFFINITY FOR OPIOIO LIGANOS" PROCEEOINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 89, no. 9, 1 May I992, pages 4I24-4I28, XP0006I5537 see the whole document	8,9,I5, 16
P,X	WO 97 24436 A (FUJII RYO ;HABATA YUGO (JP); HOSOYA MASAKI (JP); KAWAMATA YUJI (JP) IO July I997 see the whole document	I-I6
P,X	HINUMA S ET AL: "A prolactin -releasing peptide in the brain " NATURE, (1998 MAY 2I) 393 (6682) 272-6. JOURNAL COOE: NSC. ISSN: 0028-0836., XP002084793 see the whole document	I-I6
T	OATABASE MEOLINE US NATIONAL LIBRARY OF MEOICINE (NLM), BETHESOA, MO, US BUGGY J J: "Binding of alpha-melanocyte-stimulating hormone to its G-protein-coupled receptor on B-lymphocytes activates the Jak/STAT pathway." XP002084796 see the whole document & BIOCHEMICAL JOURNAL, (I998 APR I) 33I (PT I) 2II-6. JOURNAL COOE: 9YO. ISSN: 0264-602I., ENGLANO: United Kingdom	I,4-7, IO-I4
A	SREEOHARAN E.A.: "Cloning and functional rxpression of a human neuroendocrine VIP receptor" BIOCHEM.BIOPHYS.RES.COMMUN., vol. 193, no. 2, I5 June I993, pages 546-553, XP002084794 see the whole document	I,4-7, IO-14
A	WO 97 083I7 A (CHIRON CORP ;OUHL OAVIO (US)) 6 March I997 see abstract	1-16

I

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 98/02765

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9605310 A	22-02-1996	CA 2196788 A	22-02-1996
		EP 0776367 A	04-06-1997
WO 9724436 A	10-07-1997	AU 1208497 A	28-07-1997
		EP 0870020 A	14-10-1998
		JP 10146192 A	02-06-1998
WO 9708317 A	06-03-1997	AU 7011896 A	19-03-1997

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2472WO0P		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP98/02765	22/06/1998	23/06/1997
International Patent Classification (IPC) or national classification and IPC C07K14/575		
Applicant TAKEDA CHEMICAL INDUSTRIES, LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/12/1998	15.09.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Chavanne, F Telephone No. +49 89 2399 8399

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP98/02765

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report* as *"originally filed"* and are not annexed to *the report since they do not contain amendments.*):

Description, pages:

1-172 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/61-61/61 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1, 5.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☒ the claims, or said claims Nos. 1, 5 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 13-16
	No:	Claims 2-4, 6-12
Inventive step (IS)	Yes:	Claims
	No:	Claims 2-4, 6-16
Industrial applicability (IA)	Yes:	Claims 2-4, 6-13, 15
	No:	Claims 14, 16

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 1 lacks clarity due to the expression "an agent". This expression is not suitable to define the scope of the claim, because there is no technical characterisation of said compound.
Moreover, the ligand polypeptide described in the present application promotes prolactin secretion. There are no indication in the specification that said ligand may modulate (promote and inhibit) or inhibit prolactin secretion. Thus, an evaluation of claims 1 and 5 in regard to novelty and inventive step cannot be carried out.

IV. Lack of unity of invention

The problem underlying claims 1-7 and 10-14 can be regarded as the provision of an agent comprising a ligand peptide which modulates prolactin secretion, the use of said ligand and a method for modulating prolactin secretion by using said ligand, whereas the problem underlying claims 8, 9, 15 and 16 can be seen in the provision of an agent comprising a ligand peptide which modulates placental function, the use of said ligand, and a method for modulating placental function by using said ligand.
These two problems differ from one another in that they are not linked by a single inventive concept because the agents claimed in these two groups of inventions are not necessarily the same. In order to render the claims allowable under Rule 13.1-13.3 PCT the sequence ID. No. 73 should be introduced into claims 1, 8 and 12-16. In the present preliminary phase, the applicant will not be invited to additional fees. However, should the application enter the European regional phase an objection under the corresponding Article will be raised.
Correspondingly, the subject-matter of claims 1-7 and 10-14, and 8, 9, 15 and 16 are not linked by a single inventive concept. Therefore, these claims lack unity *a priori* (Rule 13(1) PCT).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive

step or industrial applicability; citations and explanations supporting such statement

1. The examination of the present application has been performed assuming that the claimed priority is valid. It is noted that intermediate documents would then become relevant to assess the patentability of any claimed subject matter not entitled to said priority.

2. Reference is made to the following documents:

   D1: American Journal of Physiology
   Vol. 272, E282-7, 1997
   D2: Proc. Natl. Acad. Sci. USA
   Vol. 89, pp. 4124-4128, 1992

3. D1 describes a polypeptide, the alpha-melanocyte-stimulating hormone (alpha-MSH), which binds to rat pituitary cells to induce prolactin secretion.
   It is implicit for such a hormonal intracellular transduction signal to be mediated by a G protein-coupled receptor protein. D1 does not specifically teach the amino acid sequence of the alpha-MSH. However, at present it cannot be ruled out that the ligand polypeptide taught in D1 has the same amino acid sequence of the ligand polypeptide of the present application, since they have similar characteristics: their binding to the rat pituitary cells induces an increase of prolactin secretion (see description, example 46). In this connection it is pointed out that as a general rule, the elucidation of a novel feature (e.g. amino acid sequence) of a known product is not able to reinstate its novelty. Thus, in view of D1, claims 2-4 are not novel. Moreover, claims 6, 7 and 12 do not contain any technical feature. Said claims attempt to define their subject-matter in terms of a result to be achieved ("for inhibiting...", "for treating or preventing..."), which is not sufficient to render it novel. Thus, claims 6, 7 and 12 are not novel. Therefore, claims 2-4, 6, 7 and 12 do not meet the requirements of Article 33(2) PCT.

4. D2 discloses polypeptides that bind to the G protein-coupled receptor protein from human placenta (see e.g. abstract). Because said polypeptides bind to the human placenta, they implicitly modulate placental function.

Thus, in view of D2, claim 8 is not novel.
Claims 9-11 as formulated do not contain any technical feature. They only attempt to define their subject-matter in terms of a result to be achieved ("for treating...", "for promoting...", "for an aphrodisiac"), which is not sufficient to render said subject-matter novel. Therefore, claims 8-11 do not meet the requirements of Article 33(2) PCT.

5. The use and methods of claims 13-16 are not specifically disclosed in the prior art. Thus, said claims appear to be novel. However, the use of a known product according to known methods, and known methods based on a known product are not inventive. Thus, claims 13-16 are not inventive.
Therefore, these claims do not meet the requirements of Article 33(3) PCT.

VI. Certain documents cited

Certain published documents (Rule 70.10)

1. WO 97/24436
2. Nature
Vol. 393, pp. 272-276, 1998

VII. Certain defects in the international application

1. Independant claims 1 and 8 both refer to an agent comprising a ligand polypeptide for a G protein-coupled receptor protein. Although claims 1 and 8 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only in that said agent modulates either prolactin secretion or placental function.
Thus, it appears appropriate to amend said claims by defining the relevant subject-matter in terms of one single independent claim followed by dependent claims covering the optional features (Rule 6.4 PCT) (see also item IV of the present communication).

VIII. Certain observations on the international application

1. Claims 1, 4-10 and 12 relate to an agent comprising a polypeptide which binds to a G protein-coupled receptor protein. These claims attempt to further define said agent in terms of a result to be achieved ("for modulating...", "for promoting...", "for inhibiting...", "for treating or preventing..."). Such a definition is only allowable under the conditions elaborated in the PCT Guidelines C-III, 4.7a. In this instance, however, it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved. Therefore, claims 1, 4-10 and 12 do not meet the requirements of Article 6 PCT.

2. The present application describes a ligand polypeptide for G protein-coupled receptor protein and shows the influence of this polypeptide on prolactin secretion (examples 46, 47, 49). All experiments show that said polypeptide promotes prolactin secretion and none of them give any indication that it might inhibit prolactin secretion. Thus, claim 5 is not supported by the description (Art. 6-support PCT). This, also applies to claim 1, because the expression "modulating" suggests that the agent of claim 1 may as well promote as inhibit prolactin secretion.

3. Claim 2 lacks clarity in that the expression "substantial equivalent" does not clearly define the scope of the claim. Said expression is without technical significance and its vagueness makes it entirely open to individual interpretation. Thus, claim 2 does not meet the requirements of Article 6 PCT.

4. For the assessment of the present claims 14 and 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.